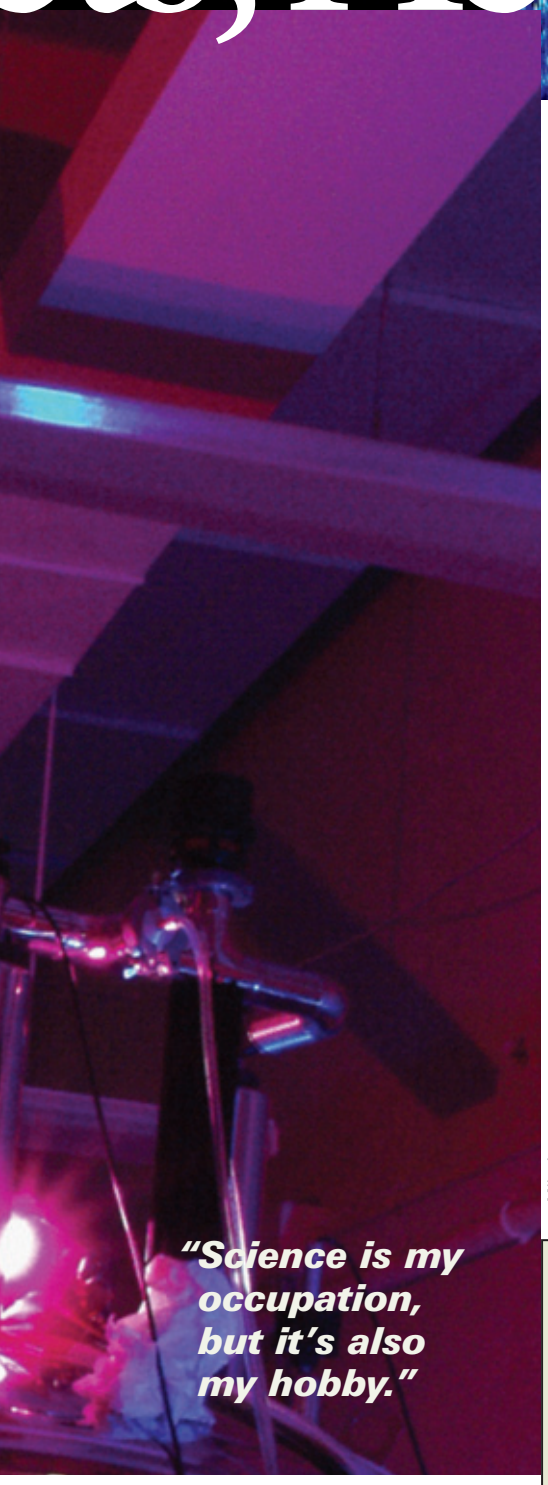
Enzymes, Magne

ets, Action!

Mike Lovett



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"Science is my occupation, but it's also my hobby."

Dorothee Kern is a biophysicist at Brandeis University in Waltham, Massachusetts. Kern studies the action of enzymes using a technique called NMR spectroscopy.

By Alisa Zapp Machalek

The point guard breaks free with the ball, dribbles past the defenders, jumps, shoots and—*swish*—two points!

Like star basketball players, worker molecules called enzymes grab, move, and stretch to carry out chemical reactions inside our bodies.

So says Dorothee Kern, a biophysicist at Brandeis University in Waltham, Massachusetts. And she should know. Previously a professional basketball player in the former East Germany, Kern, 37, now examines in fine detail the actions of enzymes. She has found that during chemical reactions, these talented molecules get entirely into the action, much like basketball players who use not only their arms to shoot the ball, but also their eyes to see the basket and their legs to jump up to it.

As a basketball player turned researcher, Kern is "the most energetic scientist I've ever known," says biophysicist Christopher Miller, whose lab is next door to Kern's. "She has a kind of hyperactivity, but a focused hyperactivity. … It's a rare combination and very fun to watch."

Behind the Iron Curtain

Kern says she forged her life path in direct response to the political situation in her homeland. A well-rounded athlete who enjoyed swimming, track and field, and other team sports, she chose to focus on basketball because it wasn't an Olympic sport. In Communist East Germany, she says, coaches of Olympic sports required their athletes "to practice all the time and take a lot of steroids." Because Kern always put school-work before sports, she says basketball was perfect for her.

"It was very competitive, but I could still go to school and get my degree in the normal time period."

Basketball was also more than just a physical game for Kern—it was an intellectual one. For 10 years, she played point guard, first for the East German team and then for the United German National team.

According to Kern, as point guard she was "the thinker on the court." It was her job to plan the plays. She traveled all over the world playing in international tournaments, including some in which she was pitted against the United States.

In addition to influencing Kern to focus on basketball, her objections to Communist ideology also solidified her decision

Enzymes, Magnets, Action!

to pursue a career in science. "I grew up behind the Iron Curtain," she says, where the political and economic system was, in her words, "bizarre." To her, science seemed less vulnerable to politics.

"In science, facts are facts. They can't be twisted easily," she says.

Having a scientific family didn't hurt either. Both of Kern's parents are chemists, her older brother is a physician, and her younger brother is a physicist.

"We used to have arguments over dinner about how to explain what's going on in nature," she chuckles. "My whole family is interested in scientific questions."

An Atomic Radar Gun

The question that intrigues Kern now is how enzymes jiggle around when they carry out, or "catalyze," chemical reactions. An enzyme is a molecule (usually a protein) that works by latching onto another molecule, known as a substrate, and causing a chemical change in it.

Often, the backdrop for Kern's experiments is a three-dimensional structure of the enzyme protein she is studying. These structures are "molecular pictures" that are usually determined with a technique from physics called X-ray crystallography. Kern likens such a structure to a snapshot of a basketball player in action. The photo may show the shape and size of a player, but it doesn't demonstrate her speed, agility, skill, or strategy. In the same way, an X-ray crystallographic structure is just a starting point for Kern.

Dorothee Kern

Before becoming a scientist, Kern (with ball) was a professional basketball player in what was then East Germany.

"We need to go beyond static structures to understand how proteins are working," she emphasizes.

True to her own active nature, Kern is interested in a protein's action or "dynamics."

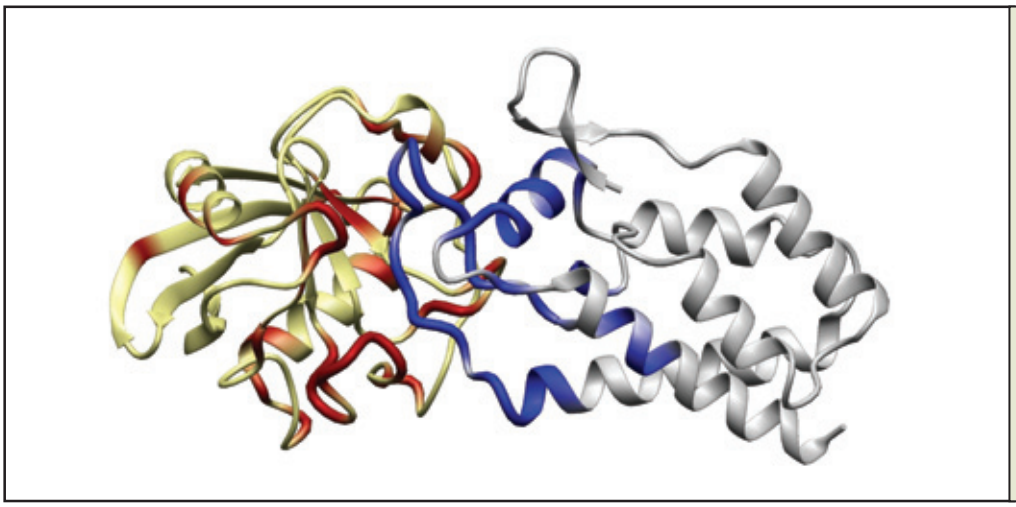
"A little bit of this interest comes because I love sports," she laughs. "Usually, I start my talks with a movie of a basketball game and say, 'that's protein dynamics' demonstrated [on a large scale]."

To study protein dynamics at the molecular level, Kern uses a technique well suited for such work—nuclear magnetic resonance (NMR) spectroscopy. This technology is based on the same physical principles as the magnetic resonance imaging (MRI) machines that doctors use to visualize organs such as the brain, heart, and kidneys. NMR is capable of detecting even the most fleeting movements within molecules. And it can simultaneously measure the motion of many different atoms in a molecule.

Kern has made some remarkable discoveries about the action of a medically important molecule called human cyclophilin A. This protein was originally identified as the molecular target of cyclosporine, a drug that is used by doctors to prevent immune rejection of transplanted organs. A better understanding of how cyclophilin A works may enable researchers to improve life-saving cyclosporine medications.

Since its initial discovery years ago, researchers have learned that human cyclophilin A can do other things. For example, the molecule can be commandeered by HIV, the virus that causes AIDS. Without cyclophilin A, HIV cannot replicate normally within cells. If scientists could find a way to cripple the interaction between HIV and cyclophilin A, they might be able to slow the spread of the virus in people infected with it.

In addition to having clinical relevance, cyclophilin A and related enzymes pique the interest of basic researchers like Kern. These molecules are found in many tissues in the human body and in "simpler" creatures all the way down to bacteria. Scientists suspect that these enzymes play essential roles in getting newly minted proteins to fold properly and in facilitating communication within cells.



Dorothee Kern

One of HIV's proteins (HIV capsid, silver) attaches to the cyclophilin A protein (gold), helping the AIDS virus spread throughout an infected person's body. Kern discovered which portions of the proteins move (blue, red) during this reaction.

Like every protein, cyclophilin A is made of a chain of amino acids. As proteins go, cyclophilin A is quite small, consisting of only 160 amino acids. It catalyzes a reaction called isomerization, in which cyclophilin A flips a part of its substrate 180 degrees, rather like flipping a light switch from an "up" position to a "down" one. And it does this with lightning speed—about 5,000 times per second.

Kern's research team uses NMR to examine the cyclophilin enzyme while it is in its resting, inactive state, as well as when the protein is in action. The researchers do this by supplying the enzyme with varying amounts of substrate. Using NMR, Kern was expecting to get a broad-brush impression of which areas of an enzyme stretch and bend the most. But even better than discovering such "dynamic hot spots," she and her coworkers found that they could use NMR like a radar gun to measure exactly how fast specific atoms in a protein move during a chemical reaction, clocking their speed in microseconds, or thousandths of a second.

Mike Lovett

Kern's research team includes two undergraduates, five graduate students, and two postdoctoral researchers.

Kern was the first scientist to simultaneously measure the movement of many atoms within an enzyme as it catalyzed a chemical reaction. She says that if you consider the protein to be a basketball player, this is like being able to see the movement of each finger and toe.

Initially, Kern identified a handful of amino acids that appear to be involved in grabbing the substrate and one that is necessary to actually flip the substrate switch. Now, as she refines her experiments, she continues to detect movement in new areas of the cyclophilin A molecule. At last count, about 30 amino acids wiggle around when cyclophilin A grabs its substrate, and at least 10 flutter while the enzyme performs its chemical reaction.

Kern's ultimate goal is to understand every quiver and flutter of cyclophilin A so well that she can make a "movie" of the molecule as it carries out its reaction. Watching such a movie would not only teach scientists—in atom-by-atom detail—about the actions and interactions of human cyclophilin A, but it would also shed light on the behavior and properties of many other enzymes.

To that end, Kern is also using NMR techniques to examine the movement of other proteins, including a cancer-associated protein called Pin1 and a molecule called tau, which has been linked to Alzheimer's disease.

Dorothee Kern

Kern and her husband, a biochemist, enjoy hiking, skiing, and many other outdoor activities with their two daughters, ages 5 and 9.

Work Hard, Play Hard

If Kern has a motto, it may well be "work hard, play hard."

When asked what advice she'd give to young people considering careers in science, she responds: "Don't give up your hobbies." Kern believes having interests outside science energizes people and spurs their creativity, both of which she says are key to doing science well.

Kern certainly takes her own advice. She plays regular pick-up basketball games with Brandeis colleagues and students. She also coaches soccer, track and field, and basketball.

"She's a fanatic outdoors woman," says Miller. "She and her husband and two young kids go sea kayaking around Cape Cod, mountain climbing…[and] all sorts of daredevil things."

In order to make time for family, hobbies, and other activities, Kern stresses the importance of working productively. "Efficiency is more important than how many hours you spend in the lab."

Her own efficiency, learned early through juggling school and sports, was further honed during her graduate studies, when she was shuttling between two different countries, playing basketball games every weekend, and attending training camps and international tournaments that could last for weeks.

Kern earned an undergraduate degree, a master's degree, and a Ph.D. in biochemistry all at Martin Luther University in Halle, Germany. In 1989, one month after she began her Ph.D. program, the Berlin Wall fell.

This caused a "big, big change in the lives of everyone in East Germany," Kern remembers.

For her, it opened up a whole new world of scientific opportunity. At the time, Kern's university didn't have NMR machines that could answer the scientific questions that interested her. A professor in Sweden learned of her research and invited her to continue her studies using his NMR facility.

So began 4 years of international commuting. Kern would collect NMR data in Sweden on Tuesdays through Fridays, bring the data back to Germany to analyze it, sleep on the night ferry back and forth, play basketball games on the weekends, and attend basketball practices on Mondays.

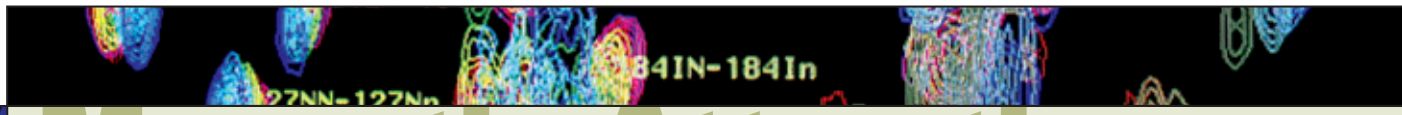
These days, Kern's schedule is still full, but less frenetic. She teaches a graduate course in enzymology and leads a research lab of 10 people. She calls this combination of teaching and research a "dream come true."

"What I'm doing is really a privilege," Kern says.

"Science is my occupation, but it's also my hobby. Compared to a lot of other people who have to work to make money, scientists work because they love it." ■

Bruce Tanner

Kern remembers clearly when the Berlin Wall was torn down, allowing her to travel freely and to interact with scientists in non-Communist countries.



Magnetic Attraction

Mike Lovett

Like many other biomedical researchers, scientists who use NMR spectroscopy rely on harmless lab bacteria to produce "labeled" proteins for their experiments. Here's how it works. First, NMR scientists need to put their bacteria on a special diet because only certain forms, or isotopes, of each chemical element contain the correct magnetic properties to be useful for NMR studies. If a researcher wants to study a protein that contains ^{13}C or ^{15}N, the two most commonly used isotopes in biological NMR research, the bacteria are fed food containing these isotopes.

Next, the scientists isolate and purify the protein they want to study and mix it in a chemical solution. They place a few drops of the protein sample into a slender glass tube. To start an experiment, they insert the tube into a powerful, specially designed magnet the size of an industrial refrigerator.

These enormous, superconducting magnets are the heart of NMR research. Cooled with liquid helium to near absolute zero (minus 460 degrees Fahrenheit), their magnetic field is hundreds of times stronger than that on Earth's surface. If you ever visit a lab containing such a magnet, you'll be told to remove your watch and wallet, because NMR magnets are notorious for stopping analog watches and erasing the magnetic data on credit card strips.

Now the special isotopes in the protein sample come into play. Tiny magnetic fields in the centers of the isotopes line up with the NMR magnet just as iron filings align on a toy magnet. The researchers blast the sample with a series of split-second, computer-controlled radio wave pulses that scramble this magnetic arrangement. By measuring the change in magnetization, researchers can analyze the movements of individual atoms within a protein. The entire process can require as little as a second for a single, simple experiment, or weeks to months for a complex molecule.—*A.Z.M.*